Clinical Center
National Institutes of Health

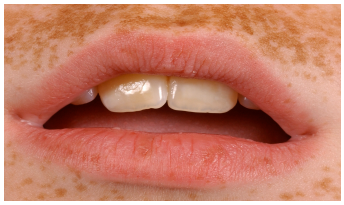
Carney Complex Patient Education Handout

What is Carney complex?

Carney complex is a genetic condition affecting many organs of the body. Carney complex was first described by Dr. J.A. Carney at Mayo Clinic in 1985 as a combination of manifestations of: 1) spotty skin pigmentation, 2) myxomas, 3) overactivity of endocrine glands, and/or 4) other tumors. People who have Carney complex often have non-cancerous tumors and skin pigmentation changes that are similar in appearance to freckles.

I. Spotty skin pigmentation

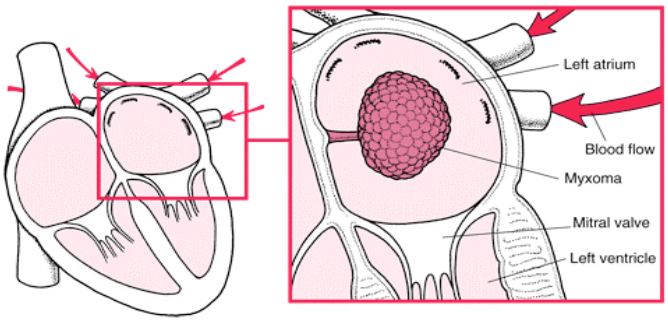
Skin: The freckle pigmentation in Carney complex is called lentigines. But unlike freckles, lentigines may be present at birth and do not darken when exposed to sunlight. They are commonly seen on the lips, eyes and mucous membranes. Lentigenes intensify with puberty but tend to fade after age 40. Other pigmented skin lesions found in patients with Carney complex are blue nevi and café-au-lait spots.



II. Myxomas

Cardiac: Myxomas (tumors of the heart) may be seen in all ages of patients with Carney complex. They may be present in the atria or ventricles of the heart. If the tumors become too large, they may require surgical removal to prevent complications like clot formation, rhythm

disturbances or heart failure. Cardiac myxomas account for a mortality rate of 25% in patients with Carney complex.



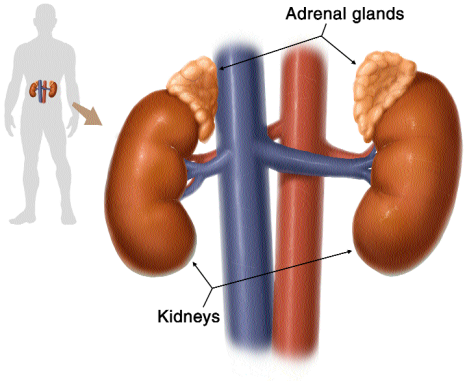
Skin: Cutaneous myxomas are small non-pigmented tumors of the skin, which may be seen as early as infancy in areas such as the eyelid, ear canal, mouth, throat, nipple and female genital area. Cutaneous myxomas of Carney complex are often associated with cardiac myxomas which, when large, impairs normal heart function.

Breast: Myxomas of the breast are often bilateral (both breasts) and are present in >70% of women with Carney complex. At NIH we identified a specialized magnetic resonance imaging (MRI) sequence in which the breast myxomas have a bright appearance that helps to distinguish them from other breast lumps. This may help prevent unnecessary breast biopsies in affected women with Carney complex.

III. Overactivity of endocrine glands

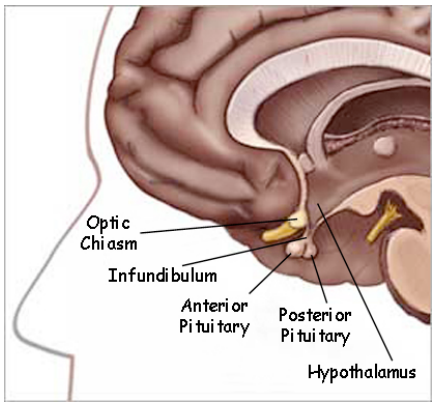
Adrenal: Adrenal glands are a pair of walnut-sized organs above the kidneys that produce hormones sending chemical messages to other organs in the body. When the adrenal glands produce too much of the hormone cortisol, the condition is called Cushing's syndrome. Primary pigmented nodular adrenocortical disease (PPNAD) is responsible for Cushing's syndrome in patients with Carney complex. Symptoms of Cushings syndrome are unexplained weight gain, abnormal fat distribution, excess hair growth, dark pink/purple stretch marks, fatigue, menstrual irregularity, decelerated growth rate in children and, if left untreated, increased risk for

development of hypertension, diabetes, and/or osteoporosis. Cushing's syndrome caused by PPNAD can be 'subclinical' or atypical with no symptoms, or periodic with symptoms which come and go.



Thyroid: Nodules may be seen as small cysts on ultrasound; in older patients these grow (they become "adenomas") and it is important to examine these nodules more closely to rule out thyroid cancer. Rarely, thyroid cancer does develop in patients with Carney complex.

Pituitary: The pituitary gland is a tiny endocrine organ found at the base of the brain. As the master gland of the body, it produces and secretes many hormones targeting other organs to produce hormones. The pituitary gland controls many of the biochemical process important to our health and well-being. Pituitary adenomas (tumors) are present in 10% to 15% of patients with Carney complex. These adenomas are known to produce the hormones growth hormone and prolactin. Elevation of growth hormone causes increase in the production of insulin growth factor-1 or IGF-1 from the liver. Elevation in IGF-1 or growth hormone causes gigantism or excessive growth (acromegaly). Excess prolactin causes cessation of the menstrual cycle in females.



Reproductive: Testicular tumors called large-cell calcifying Sertoli cell tumors (LCCSCT) occur frequently in males with Carney complex. LCCSCT appear as small calcified areas on an ultrasound of the testicles. These tumors are usually benign and may be associated with gynecomastia (breast tissue enlargement in boys and men). Other testicular tumor may also occur in males with Carney complex but they are more are than LCCSCT. Women with Carney complex may have ovarian cysts or breast ductal adenomas (located in the intraductal areas of the breast), which are typically benign. Ovarian cancer may develop rarely.

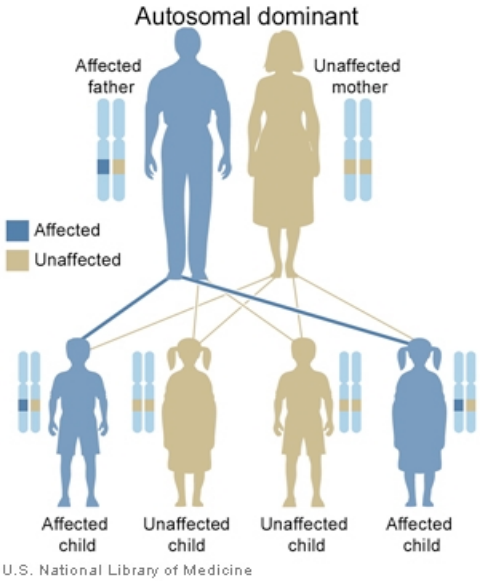
IV. Other tumors

Psammomatous melanotic schwannomas (PMS) are rare tumors (<10%) that may occur in the peripheral nervous system. Schwannomas are nerves that have an insulating coating of Schwann cells resulting in a bundled nerve appearance on imaging. They are most frequently seen in the intestinal tract and along the spinal nerves. An osteochondromyxoma or a tumor of the bone may also be associated with Carney complex, but these are rare.

How is Carney complex inherited?

An inherited disorder is one that can be passed on from the parents to their children. Carney complex is usually inherited through "autosomal dominant" transmission. Autosomal dominant inheritance of Carney complex is most often due to a faulty gene called *PRKAR1A* located on the chromosome 17. This gene is thought to be a tumor suppression gene. In some cases, Carney complex may be caused by defects in a gene (or genes) on chromosome 2. Carney complex can also occur spontaneously without any other family members having the faulty gene. These cases are referred to as "sporadic de novo mutations". When a parent has Carney complex with the autosomal dominant mutated gene, there is a 50% chance with each pregnancy that their child

will be affected by the same faulty or mutated gene. It is important that patients with Carney complex receive genetic counseling before planning a family.



Males and females are affected equally with Carney complex but some manifestations of the syndrome do vary with gender; for example, Cushing's syndrome is more common in girls and women with Carney complex.

Initial Work-Up

Screening for Carney complex involves a multisystem approach to ensure all manifestations discussed above are detected. Studies during the initial work-up include blood tests to evaluate hormone levels of the endocrine system (cortisol, growth hormone, prolactin), thyroid function, gonadotropin (reproductive), and genetic testing. To evaluate for possible abnormality of adrenal hormone production the following tests are performed: diurnal (overnight and morning) blood cortisol and ACTH levels, dexamethasone testing, and 24-hour urine collection for free cortisol, creatinine and 17-hydroxysteroids. An echocardiogram or ultrasound of the heart is performed to check for myxomas. In older children and adults, MRI of the heart is obtained to get a better

visualization of the heart to detect any myxomas. Similarly, MRI of the pituitary is also performed to detect tumors or enlargement. A computed tomography (CT) scan is performed to check the adrenal glands for hyperplasia (enlargement). MRI of the chest, abdomen, pelvis and the entire spine is performed to screen for schwannomas. The testicles, ovaries, and thyroid glands require an annual ultrasound to detect any abnormality or to follow-up on previously detected lesions.

Recommendations for Routine Screening

Puberty plays a role in determining which screening is recommended. Pre-pubertal girls and boys require close monitoring of the growth rate to detect effects of excess cortisol, growth hormone, or estrogen/testosterone. A pre-pubertal patient should receive an annual echocardiogram to examine the myxomas in the heart. This recommendation changes to **every six months**, if there are already myxoma(s) that have been surgically removed. Similarly, pre-pubertal boys should have a testicular ultrasound annually to screen or monitor for Large-cell calcifying Sertoli cell tumor (LCCSCT). For girls and women, the ovaries should be examined with ultrasound annually to detect cysts or adenomas. After puberty, these same screening tests are performed in addition to a few more: a thyroid ultrasound is performed annually to screen for nodules or adenomas. 24-hour urine collections should be obtained to test for free cortisol levels. Also, IGF-1 (insulin growth factor- 1) levels in the blood should be monitored to detect abnormalities of growth hormone production. Any tumor sites discovered at diagnosis require additional testing: if hyperplasia (enlargement) or tumors of the adrenal glands are identified, it is important to measure diurnal cortisol levels in the blood in addition to performing a dexamethasone test. Imaging should be performed to monitor adrenal gland size. If the pituitary gland is found o have a tumor, it is important to perform an oral glucose tolerance test to monitor growth hormone

levels. MRI imaging should be performed to monitor the pituitary gland. If schwannomas are discovered on initial evaluation, MRI should be performed annually to examine the brain, spine, chest, abdomen and pelvis.

Table 1: Recommended clinical surveillance

Patient	*Screening Modality*	*Frequency*
Pre-puberty	Echocardiogram	Annually Biannually (hx of excised myxomas)
	Testicular ultrasound	Annually
	Growth rate monitoring & pubertal staging	Annually
Post-puberty	Echocardiogram	Annually Biannually (hx of excised myxomas)
	Testicular ultrasound	Annually
	Urinary free cortisol levels	Annually
	Serum IGF-1 levels	Annually
	Thyroid ultrasound	Baseline (repeat as needed)
	Ovarian ultrasound	Baseline (repeat as needed)
PPNAD	Urinary free cortisol levels	Annually
	Diurnal cortisol levels	Baseline (repeat as needed)
	Dexamethasone-stimulation test	Baseline (repeat as needed)
	Adrenal CT	Baseline (repeat as needed)
Gigantism/ Acromegaly	Serum IGF-1 levels	Annually
	Pituitary MRI	As needed
	3-Hr. Oral glucose tolerance test	As needed
	Serum GH, PRL levels	Baseline (repeat as needed)
PMS	MRI of brain, spine, chest, abdomen, retroperitoneum & pelvis	Annually

How is Carney complex treated?

There is no cure for Carney complex. However, screening at the recommended intervals is important for early identification and treatment of potential endocrine dysfunction, tumors and/or myxomas. Surgery may be indicated for treatment of thyroid adenomas (or cancer) and cardiac myxomas. Tumors of the pituitary gland that produce excess growth hormone may be treated with medication, surgery, and/or radiation. Skin myxomas may sometimes require surgical removal. Excess cortisol production by the adrenal glands may require surgical treatment

(bilateral adrenalectomy), in which case lifelong replacement medications (glucocorticoid and mineralcorticoid) are needed. Boys or men with testicular calcifications or tumors (LCCSCT) may require medication (or, rarely, surgical treatment) if they produce hormones or if they are suspicious for cancer.

Can Carney complex be diagnosed prenatally?

For individuals affected with Carney complex who have a positive (known) gene mutation test result, prenatal testing can be performed for pregnancies at increased risk. Consultation with a genetic counselor is an important part of planning for pregnancy in individuals affected with Carney complex.

Do women or men with Carney complex have fertility problems?

Women with Carney complex may experience abnormality of menstrual cycles due to abnormal cortisol production or cysts of the ovaries, either of which may interfere with normal ovulation. Men affected with Carney complex with calcifications in the testes due to LCCSCT may experience problems with fertility due to obstruction of the sperm (seminiferous) tubules or by inappropriate hormone production.

What research is being done?

At NIH scientists are investigating genetic mutations that are associated with Carney complex. In addition, a clinical study at NIH and other collaborating research centers are investigating the association between genotype (genetic mutation) and phenotype (physical manifestation) of Carney complex in order to better understand the disorder and natural progression, with a goal of improved detection and treatment.

Recommended websites for additional information

http://segen.nichd.nih.gov/research_carney
http://www.ncbi.nlm.nih.gov/books/NBK1286
http://Clinicaltrials.gov

For more information:

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